

The diagram illustrates the 40S ribosomal subunit and its associated factors. At the top, a cluster of circles represents 'Insulin, growth factors' and 'BP'. Below this, a horizontal line is labeled '4E'. To the right, a vertical line is labeled 'AUG' and 'AAAA'. A diagonal line connects the '4E' label to the '4G' label. The '4G' label is positioned above a large, dark, oval-shaped structure labeled '40S'. Inside the '40S' structure, the label 'eIF3' is visible. To the right of the '40S' structure, a small, dark, oval-shaped structure is labeled '4A'. At the bottom, a horizontal line is labeled 'AUG' and 'AAAA'.

The diagram illustrates two major signaling pathways initiated by growth factors and hormones/mitogens:

- PI3K/Akt/mTOR Pathway:** Growth factors and hormones/mitogens activate PI3K, which leads to Akt. Akt inhibits mTOR. Rapamycin (an mTOR inhibitor) is shown inhibiting mTOR. This pathway leads to the phosphorylation of BP and 4E.
- Ras/Raf/MEK/ERK/Mnk-1 Pathway:** Growth factors and hormones/mitogens activate Ras, which leads to Raf, MEK, ERK, and Mnk-1. PD 098059 (a MEK inhibitor) is shown inhibiting MEK. This pathway also leads to the phosphorylation of BP and 4E.

Both pathways converge on the phosphorylation of BP and 4E, which are represented by black circles at the bottom of the diagram.

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FIGURE 3

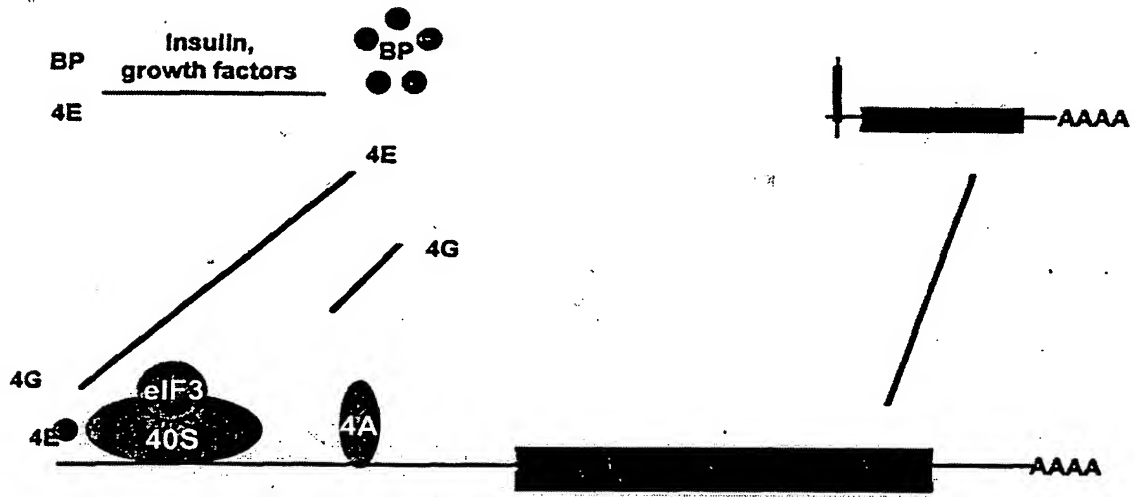
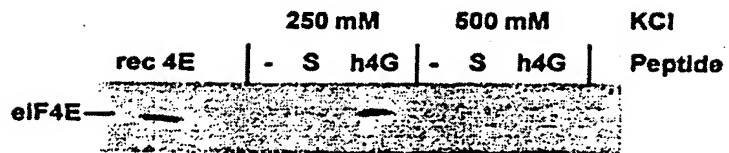


FIGURE 4



h4g human eIF4G Bβ KKRYDREFLLGFAARQIKIWFQNRRMKWKK

S scrambled eIF4G Bβ FDLKFALGRYRAEKRQIKIWFQNRRMKWKK

- no peptide

rec 4E recombinant human eIF4E

FIGURE 5

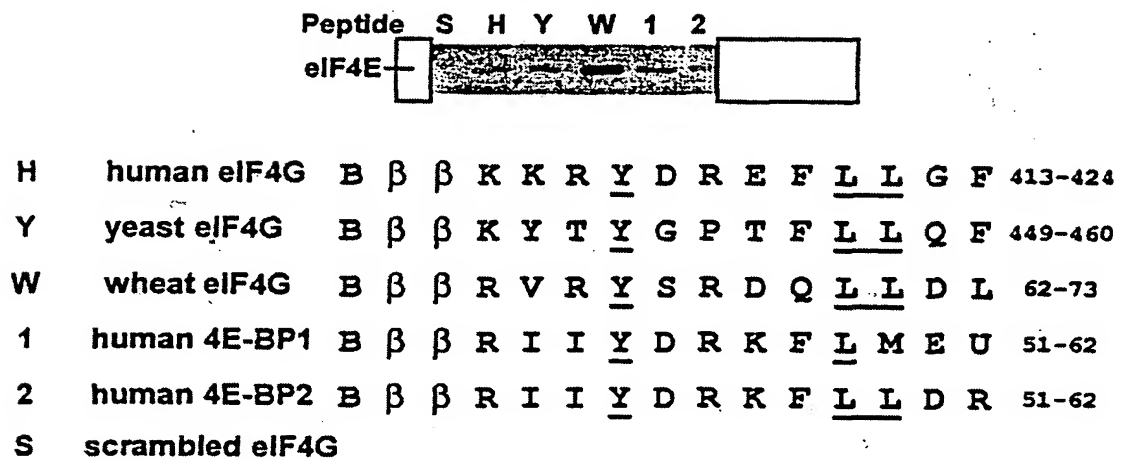
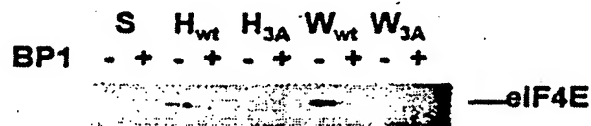


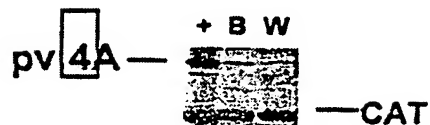
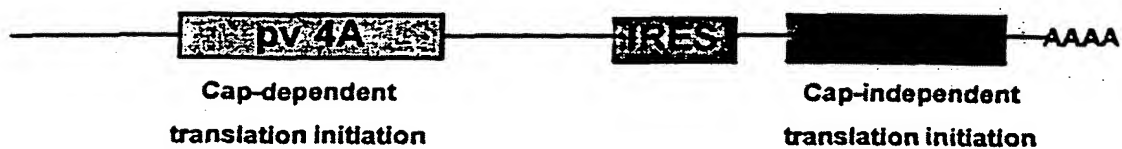
FIGURE 6



4G Peptide			Sequence														
H _{wt}	hu 4G ₍₄₁₃₋₄₂₄₎		K	K	R	<u>Y</u>	D	R	E	F	<u>L</u>	<u>L</u>	G	F	A	A	
H _{3A}	hu 4G ₍₄₁₃₋₄₂₄₎ YALALA		K	K	R	A	D	R	E	F	A	A	G	F	A	A	
W _{wt}	wh 4G ₍₆₂₋₇₃₎		R	V	R	<u>Y</u>	S	R	D	Q	<u>L</u>	<u>L</u>	D	L	A	A	
W _{3A}	wh 4G ₍₆₂₋₇₃₎ YALALA		R	V	R	A	S	R	D	Q	A	A	D	L	A	A	
S	scrambled hu 4G		F	D	L	K	F	A	L	G	R	Y	R	A	E	K	

all peptides biotinylated and linked to Penetratin™

FIGURE 7

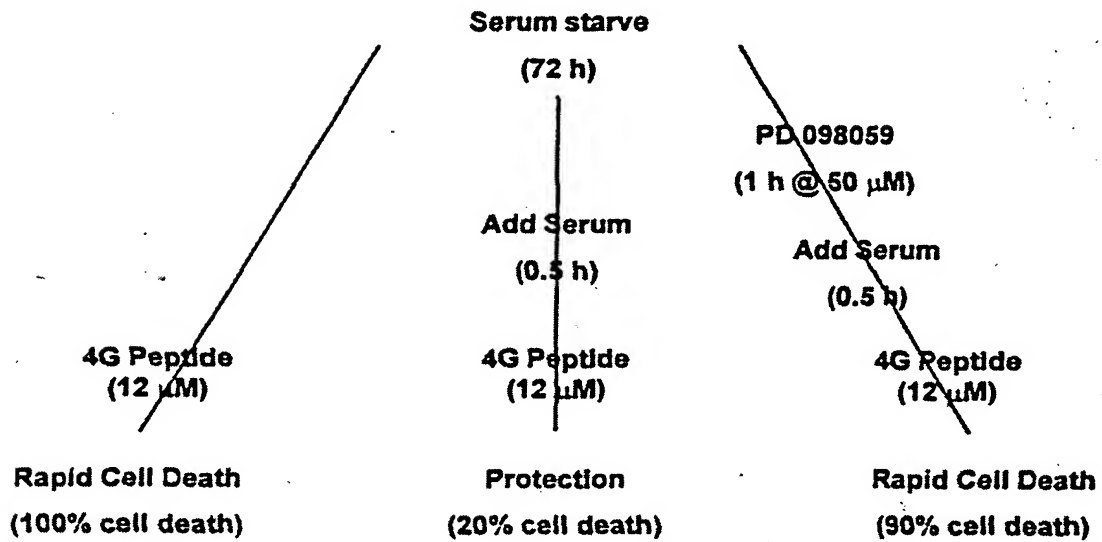
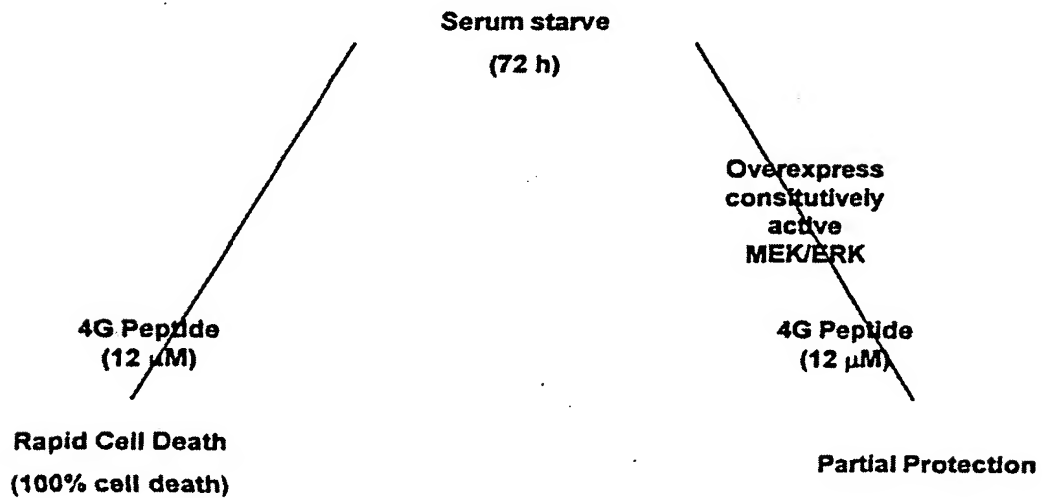


+ Positive control
 B human 4E-BP1
 W wheat eIF4G₍₆₂₋₇₃₎

FIGURE 8

Peptide	Concentration			
	3 μ M	6 μ M	9 μ M	12 μ M
hu 4G ₍₄₁₃₋₄₂₄₎	+	++	+++	+++
hu 4G ₍₄₁₃₋₄₂₄₎ Y416AL421AL422A	-	-	-	-
wh 4G ₍₆₂₋₇₃₎	-/+	+	++	+++
wh 4G ₍₆₂₋₇₃₎ Y65AL70AL71A	-	-	-	-
scrambled hu 4G	-	-	-	-

MRC5 cells, 72 h serum-free growth, all peptides biotinylated and linked to Penetratin™

FIGURE 9FIGURE 10

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FIGURE 11

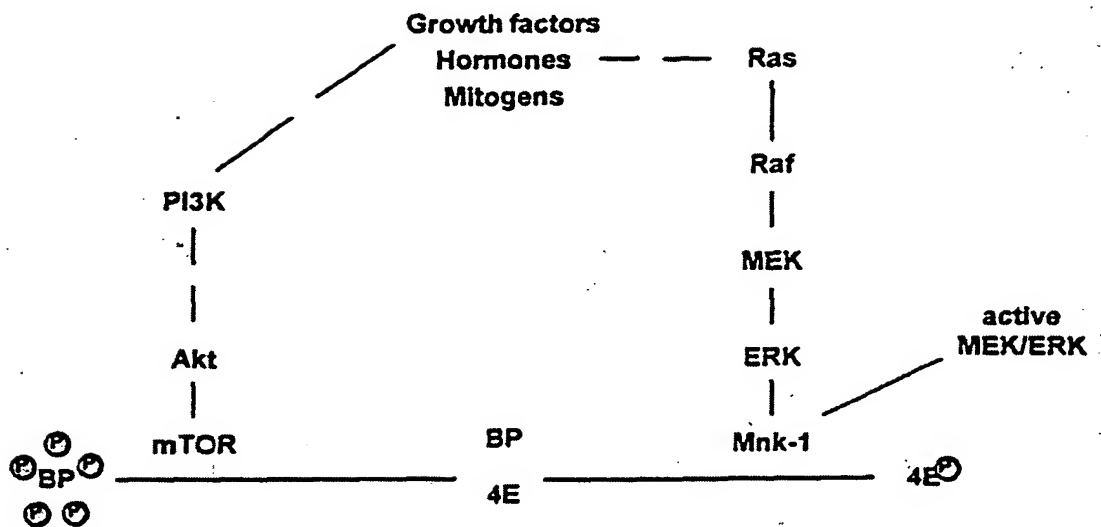


FIGURE 12

(a)

Hu 4G	Human eIF4G Peptide (569-580)Wild Type	KKRYDREFLLGF
Hu 4G YLL-AAA	Human eIF4G Peptide (569-580)Y572A L577A L578A	KKRADREFAAGF
Hu 4G Y-A	Human eIF4G Peptide (569-580)Y572A	KKRADREFLLGF
Hu 4G L-A	Human eIF4G Peptide (569-580)L577A	KKRYDREFALGF
W4G	Wheat eIF4G Peptide (62-73)Wild Type	RVRYSRDQLLDL
W4G YLL-AAA	Wheat eIF4G Peptide (62-73)Y65A, L70A, L71A	RVRASRDQAADL
BP2	Human 4E-BP2 Peptide (51-62)Wild Type	RIIYDRKFLLDR
BP2 YLL-AAA	Human 4E-BP2 Peptide (51-62)Y54A, L59A, L60A	RIIADRKFAADR
BP1	Human 4E-BP1 Peptide (51-62)Wild Type	RIIYDRKFMEU
BP1 YLM-AAA	Human 4E-BP1 Peptide (51-62)Y54A, L59A, M60A	RIIADRKFAAEU

(b)

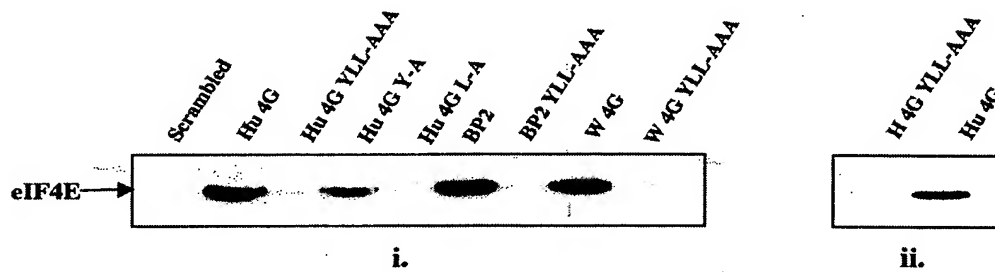
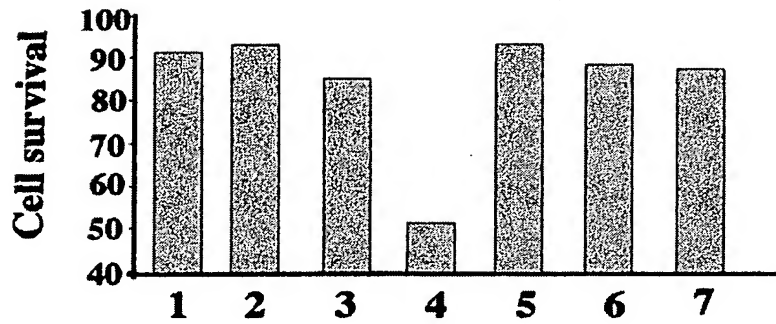
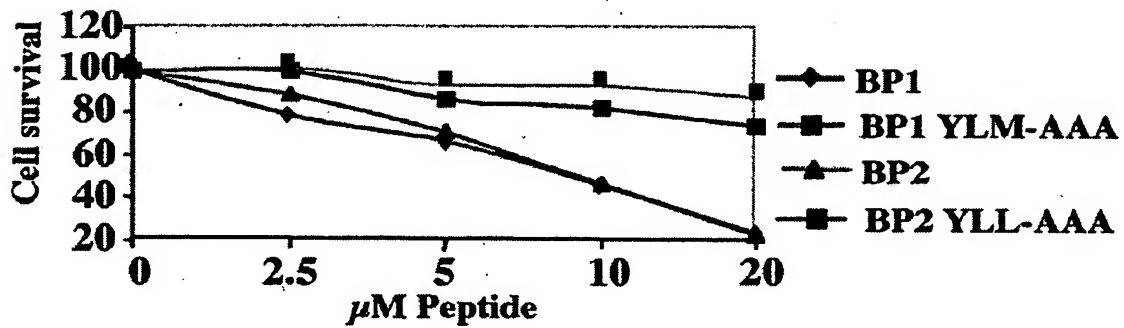


FIGURE 13

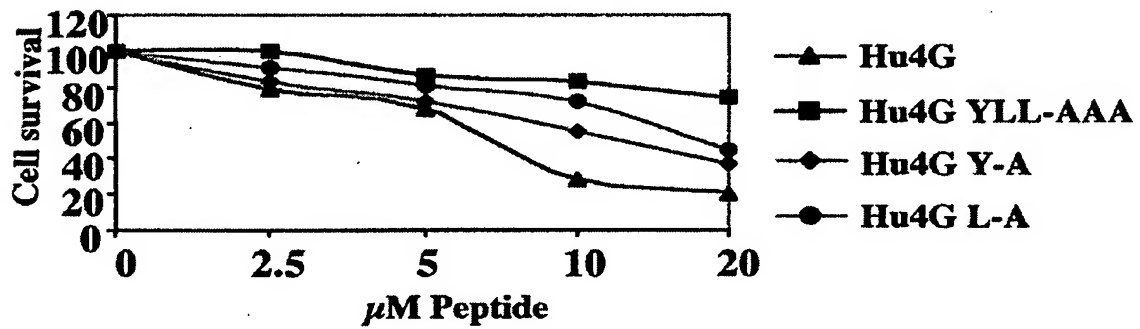
(a)



(b)



(c)



(d)

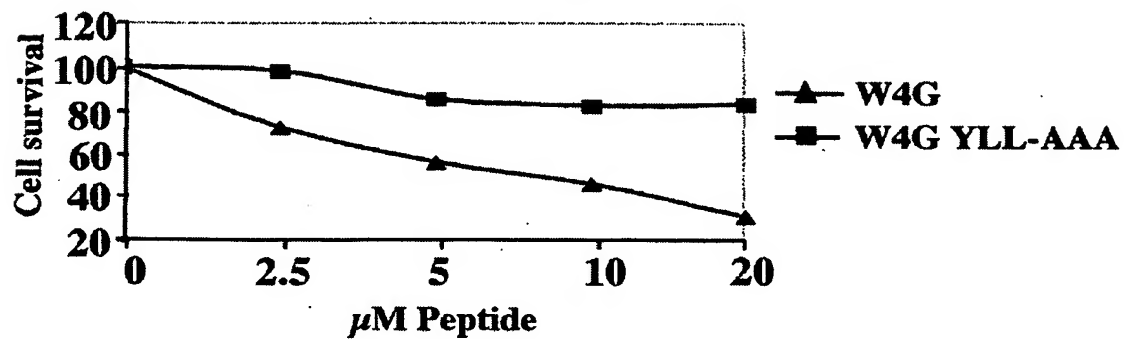


FIGURE 14

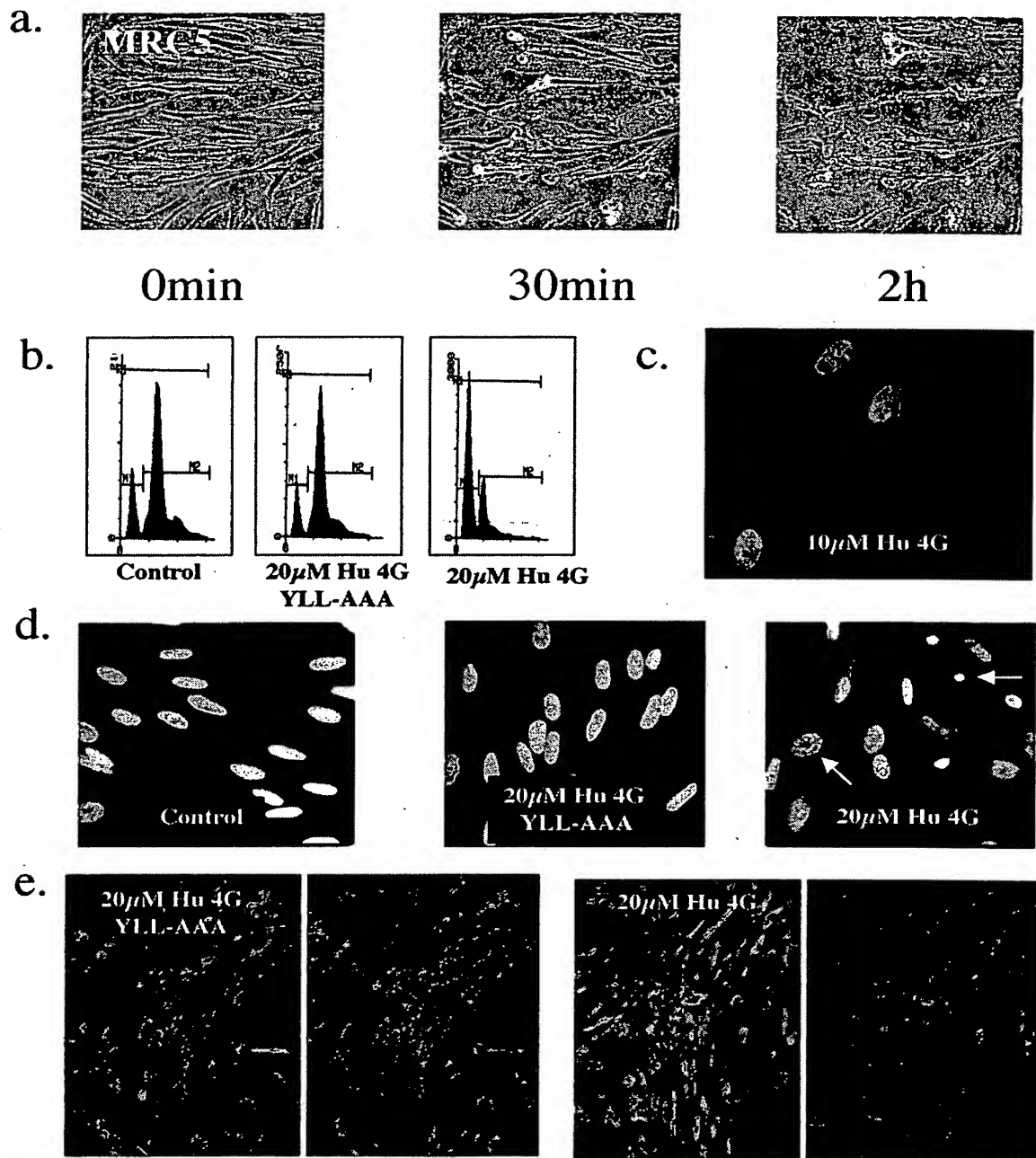


FIGURE 15

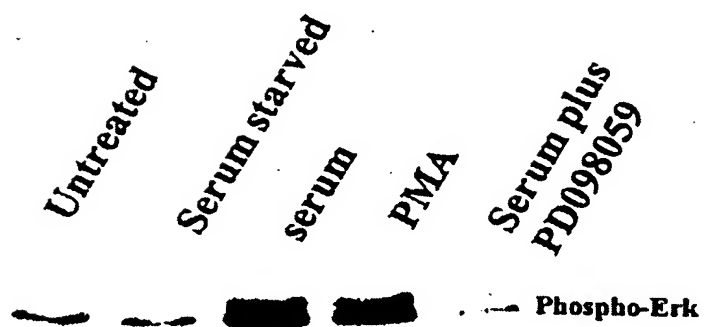


FIGURE 16

(a)

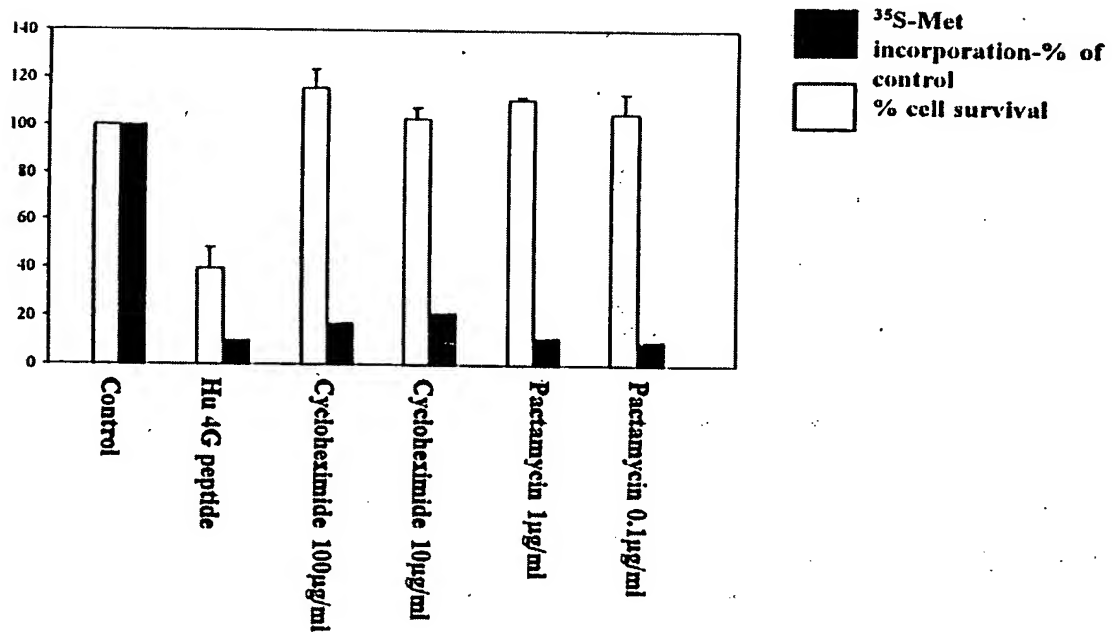
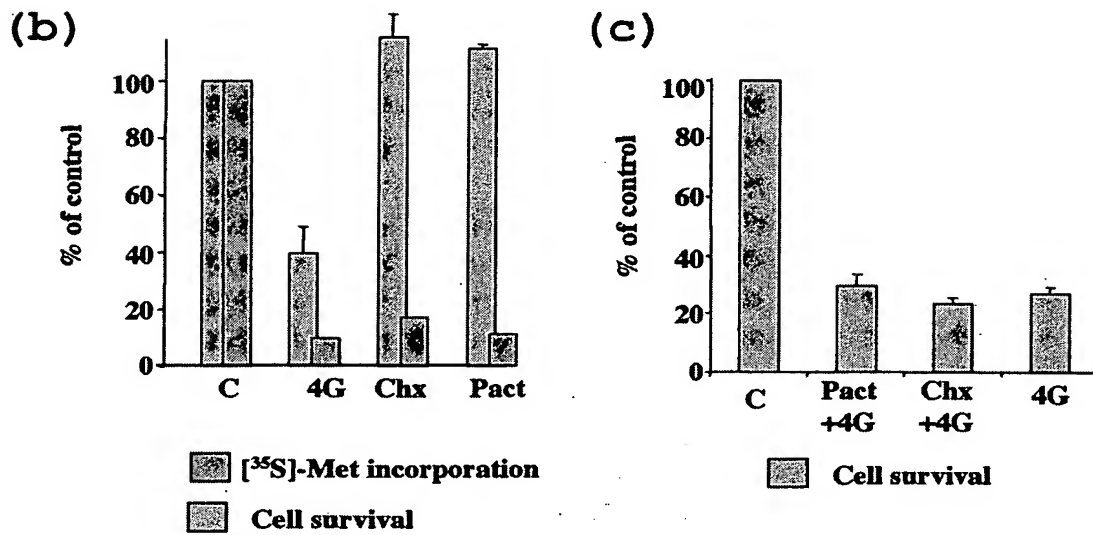


FIGURE 16(cont.)



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